

[54] **PROCESS FOR THE CROSS-LINKING OF PROTEINS**

[75] Inventors: **Menachem Rubinstein**, Kiryat Ono; **Shulamit Simon**, Ramat-Gan, both of Israel; **Rene Bloch**, deceased late of Savion, Israel, by **Rachel Bloch**, administratrix

[73] Assignee: **Research Products Rehovot Ltd.**, Rehovot, Israel

[21] Appl. No.: **695,030**

[22] Filed: **Jun. 11, 1976**

[30] **Foreign Application Priority Data**

Jun. 12, 1975 [IL] Israel 47468

[51] Int. Cl.² **C07G 7/02; C07G 7/00**

[52] U.S. Cl. **195/63; 195/68; 195/DIG. 11; 260/112 R; 260/122**

[58] Field of Search **195/63, 68, DIG.11; 260/112 R, 117, 122**

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,796,634 3/1974 Haynes et al. 195/63
4,009,267 2/1977 Huber et al. 260/112 R

OTHER PUBLICATIONS

Wold in Hirs (Editor) *Methods in Enzymology*, vol. XI (1967), pp. 617-640.

Primary Examiner—Lionel M. Shapiro

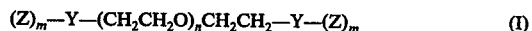
Attorney, Agent, or Firm—Millen & White

[57]

ABSTRACT

The invention relates to a process for the cross-linking of proteins wherein the proteins to be cross-linked are reacted with a cross-linking agent selected from the group consisting of:

(a) water soluble poly(ethylene oxide) derivatives of the general formula I



wherein both n and m are at least 1; Y is a covalent bond or is an —R— or —RO— radical in which the oxygen is bound to the poly(ethylene oxide) and R is selected from the group consisting of methylene, ethylene, propylene, o—, m— and p-phenylene, o—, m— and p-phenylene carbamate optionally substituted by one or more alkyl, aryl, halo, nitro, oxo, carboxy, hydroxy, thio, sulfonate and phosphate groups; and Z is a reactive group selected from the groups consisting of haloisocyanato-, isothiocyanato-, tosylate, acyl halides, acyl azides, aryl diazonium salts, acyl imidoester salts, activated esters of acyl residues and 2,4-dichlorotriazines; and

(b) activated esters of di- and poly-carboxylic acids wherein the acids and the alcohol moieties thereof are water soluble.

31 Claims, No Drawings